Trials@uspto.gov
571.272.7822

Paper No. 14
Entered: April 9, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2017-01256
Patent 9,249,149 B2

Before LORA M. GREEN, MICHAEL J. FITZPATRICK, and TINA E. HULSE, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* HULSE.

Opinion Dissenting-in-part by *Administrative Patent Judge* FITZPATRICK.

HULSE, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Incyte Corporation ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–15 of U.S. Patent No. 9,249,149 B2 (Ex. 1001, "the '149 patent"). Paper 1 ("Pet."). Concert Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

We denied institution of an *inter partes* review of all challenged claims on all three grounds asserted. Paper 9, 20. Petitioner filed a Request for Rehearing of the two obviousness grounds it had asserted (i.e., Grounds 1 and 3). Paper 12. We granted the Request for Rehearing in a separate Decision concurrently entered with the instant Decision. Paper 13.

An *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On rehearing, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–15 of the '149 patent. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The parties identify pending U.S. Patent Application No. 14/570,954 as a related matter to this proceeding. Pet. 1; Paper 5, 1. The '149 patent is a continuation of that application.

B. The '149 Patent

The '149 patent is titled, "Deuterated Derivatives of Ruxolitinib," which issued on February 2, 2016. Ex. 1001, (54), (45). The earliest possible filing date to which the challenged claims could be entitled is June 15, 2012. *Id.* at (60).

According to the ’149 patent, many current medicines suffer from poor adsorption, distribution, metabolism, and/or excretion (“ADME”) properties that limit their use for certain indications. *Id.* at 1:20–23. For example, rapid metabolism can cause drugs to be cleared too rapidly from the body, decreasing the drugs’ efficacy in treating a disease. *Id.* at 1:28–31. Another ADME limitation is the formation of toxic or biologically reactive metabolites. *Id.* at 1:39–40.

The cytochrome P450 enzyme (“CYP”) is typically responsible for hepatic metabolism of drugs. *Id.* at 1:52–54. As such, the ’149 patent identifies deuterium modification as a “potentially attractive strategy for improving a drug’s metabolic properties.” *Id.* at 2:5–6. Deuterium modification involves replacing one or more hydrogen atoms of a drug with deuterium atoms in an attempt to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites. *Id.* at 2:6–10. Because deuterium forms stronger bonds with carbon than hydrogen, in certain cases, that stronger bond strength can positively impact the ADME properties of a drug, resulting in the potential for improved drug efficacy, safety, and/or tolerability. *Id.* at 2:11–15.

According to the ’149 patent, however, studies measuring deuterium substitution’s effect on overall metabolic stability have reported variable and unpredictable results. *Id.* at 2:32–35. The ’149 patent explains that the effects of deuterium modification on a drug’s metabolic properties are not predictable “even when deuterium atoms are incorporated at known sites of metabolism.” *Id.* at 2:42–44. As such, the specification states that determining whether and how deuterium modification affects the metabolism rate of a drug requires actually preparing and testing the deuterated drug. *Id.* at 2:44–47. Thus, the ’149 patent states that “[t]he

site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug." *Id.* at 2:49–52.

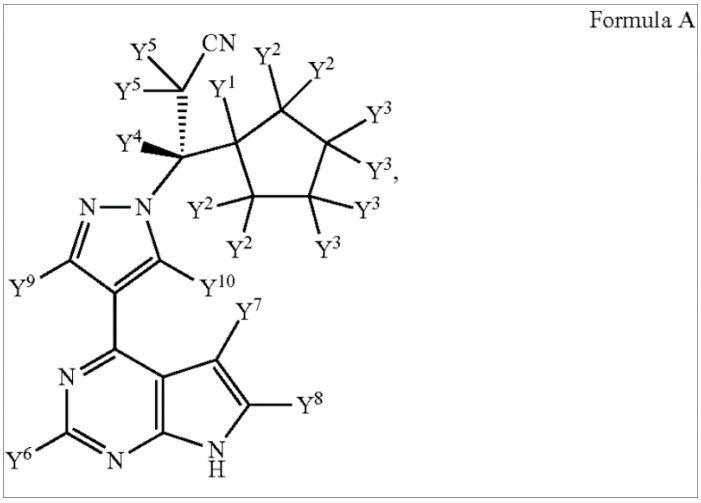
Ruxolitinib phosphate, a heteroaryl-substituted pyrrolo [2,3-d]pyrimidine, is an FDA-approved drug for treating patients with intermediate or high-risk myelofibrosis. *Id.* at 2:66–67. Ruxolitinib also has other potential applications, including the treatment of essential thrombocytopenia, psoriasis, and various forms of cancer. *Id.* at 3:3–6. Thus, according to the specification, "[d]espite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions." *Id.* at 3:19–21.

C. Illustrative Claim

Petitioner challenges claims 1–15 of the '149 patent, of which claims 1 and 9 are the only independent claims. Claim 1 is illustrative and is reproduced below:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is a hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9, and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

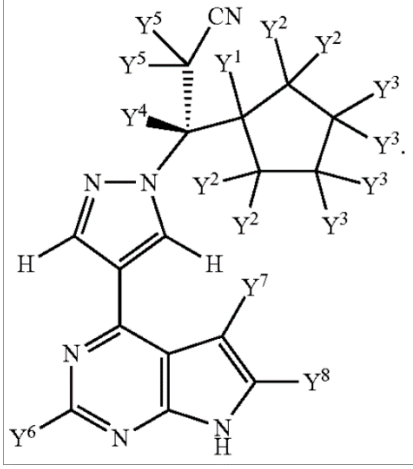
each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Ex. 1001, 36:17–53.

Claim 9 is similar to claim 1, but is directed to Formula I, which is reproduced below:

Formula I



Formula I is similar to Formula A, but Y^9 and Y^{10} of Formula A are both hydrogen in Formula I.

Claims 2–7 and 10–14 depend from claim 1 or claim 9 and recite specific deuteration patterns of ruxolitinib. Claims 8 and 15 depend from

claim 1 and claim 9, respectively, and recite a pharmaceutical composition of claim 1 or claim 9, and a pharmaceutically acceptable carrier.

D. Asserted Grounds of Unpatentability on Rehearing

On rehearing, Petitioner challenges the patentability of claims 1–15 of the '149 patent on the following grounds:

Reference(s)	**Basis**	**Claims challenged**
Jakafi Prescribing Information,[1] Shilling,[2] and the Concert Backgrounder[3]	§ 103	1–15
Rodgers,[4] Shilling, and the Concert Backgrounder	§ 103	1–15

Petitioner also relies on the Declaration of F. Peter Guengerich, Ph.D. (Ex. 1002).

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art as of June 15, 2012, would have had a "master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline," or a lesser degree with more experience. Pet. 9 (citing Ex. 1002 ¶¶ 15–18). Patent Owner does not contest

---

[1] Jakafi Prescribing Information (revised 11/2011). ("Jakafi Label," Ex. 1004),

[2] Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase ½ Inhibitor, in Humans*, 38 DRUG METABOLISM AND DISPOSITION 2023–31 (2010) ("Shilling," Ex. 1005).

[3] CoNCERT Pharmaceuticals, Inc. Precision Deuterium Chemistry Backgrounder ("Concert Backgrounder," Ex. 1006).

[4] Rodgers et al., US 7,598,257 B2, issued Oct. 6, 2009 ("Rodgers," Ex. 1007).

Petitioner's definition of the level of ordinary skill in the art in its Preliminary Response. Prelim. Resp. 27.

On this record, we adopt Petitioner's uncontested definition of the level of ordinary skill in the art. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

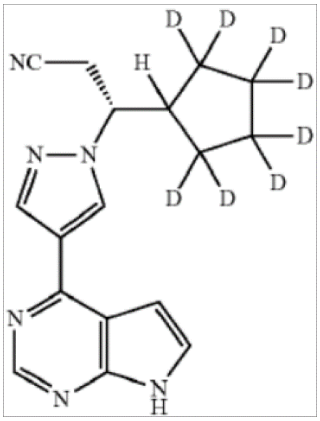
B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

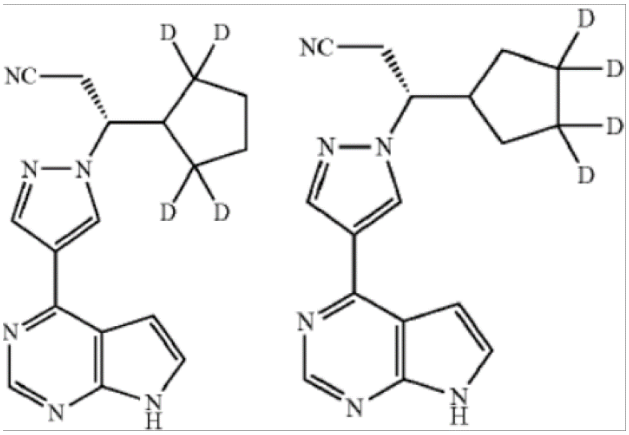
We determine that it is unnecessary to expressly construe any claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting

Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999)).

We note, however, that Petitioner limits its analysis to three compounds that it contends are covered by each of the claims. Specifically, Petitioner asserts that claims 1, 2, 5–7, 9, 10, 13, and 14 each read on the following "octa-deuterated" ruxolitinib analog, illustrated below:



Pet. 8. Petitioner also asserts that claims 1–4, 6, 7, 9–12, and 14 each read on the following "tetra-deuterated" ruxolitinib analogs, illustrated below:



Id. Patent Owner does not dispute Petitioner's contention.

Having considered the compounds and the claims, we agree with Petitioner that the cited claims encompass the three compounds.

C. 35 U.S.C. § 325(d)

Under 35 U.S.C. § 325(d), the Board may reject a petition because "the same or substantially the same prior art or arguments previously were presented to the Office." *Id.* Patent Owner argues that we should exercise our discretion and deny the Petition because Petitioner's obviousness arguments are substantively the same as those already considered and rejected during prosecution. Pet. 25–27, 48–52.

The Board recently designated *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586 (PTAB Dec. 15, 2017) (Paper No. 8) as an informative decision that provides a nonexhaustive list of factors the Board has considered in the past when evaluating whether to apply § 325(d). *Id.* at 17–18. Such factors include the similarities and material differences between the asserted art and the prior art involved during examination; the extent to which the asserted art was evaluated during examination; whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments. *Id.*

Having considered the prosecution history of the '149 patent, we are not persuaded that we should exercise our discretion to deny institution under the facts of this case. We acknowledge that each of the asserted references except Concert Backgrounder was presented to the examiner during prosecution. Applicants presented Rodgers and Shilling in an Information Disclosure Statement, which the examiner considered. Ex. 1009, 81, 121. And Applicants' declarant, Vinita Uttamsingh, cited Jakafi Prescribing Information in her Rule 132 declaration. *Id.* at 286 ¶ 4 (Ex. A). Only Rodgers, however, served as a basis for an obviousness

rejection by the examiner, along with a number of other secondary references. *Id.* at 105–08.

To overcome the obviousness rejection, Applicants relied on the Uttamsingh declaration to demonstrate unexpected results. *Id.* at 253–54, 285–88. In her declaration, Ms. Uttamsingh describes the results of various studies conducted under her supervision comparing the in vitro metabolism of ruxolitinib with that of the claimed compounds. *Id.* at 285–87. She concludes that the studies show that the claimed compounds are metabolically more stable than ruxolitinib in the in vitro assays, and that the results "could not have been predicted by any person knowledgeable of the [Drug Metabolism and Pharmacokinetics] field." *Id.* at 287.

Through the testimony of its declarant, however, Petitioner contests the results of the Uttamsingh studies and her conclusion that those results were unexpected. Dr. Guengerich testifies that, in his opinion,

> [T]hese results were not probative of unexpected results because (1) a [person of ordinary skill in the art] would have expected at least some *in vitro* effect from deuterating at the cyclopentyl metabolic 'hot spot' of ruxolitinib; (2) the experimental parameters were not probative of how the tested analogs would actually perform *in vivo*; (3) the magnitude of [kinetic isotope effect] in the *in vitro* tests was not unexpectedly superior based on the [kinetic isotope effects] shown in the art; and (4) the experiments were not commensurate with the scope of the claims.

Ex. 1002 ¶ 118; *see also id.* ¶¶ 119–129. Thus, unlike the petitioner in *Becton*, here Petitioner directly addresses the arguments and evidence submitted during prosecution through the testimony of its declarant. *See Becton*, slip op. at 24–25 ("Petitioner has not pointed to error by the Examiner, or for that matter addressed the evidence and argument presented by Patent Owner, during the underlying prosecution of the [involved]

patent."). We find Petitioner's effort to address the applicants' unexpected results evidence in the Petition outweighs the fact that Rodgers was considered and relied upon by the Examiner during prosecution.

Taking the facts and circumstances of this proceeding as a whole, we decline to exercise our discretion to deny the Petition under § 325(d).

We now turn to the substantive challenges to the claims.

D. Obviousness over Jakafi Label, Shilling, and Concert Backgrounder

Petitioner asserts that claims 1–15 of the '149 patent are unpatentable as obvious over the combination of Jakafi Label, Shilling, and Concert Backgrounder. Pet. 26–43. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 27–59. On this record, we determine that Petitioner has not established a reasonable likelihood of prevailing on this assertion.

1. Jakafi Label (Ex. 1004)

Jakafi Label provides prescribing information for JAKAFI (ruxolitinib). Ex. 1004, 1. Jakafi Label states "Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis" and provides information such as dosage and administration, contraindications, adverse reaction, and drug interactions. *Id.*

2. Shilling (Ex. 1005)

Shilling teaches that ruxolitinib is a "potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, Abstract. Shilling discloses a study of the metabolism, excretion, and pharmacokinetics of ruxolitinib. *Id.* In its study, Shilling identifies two major metabolites of ruxolitinib: M18 (2-hydroxycyclopentyl ruxolitinib) and M16/M27 (3-hydroxycyclopentyl ruxolitinib). *Id.* at 2030.

3. Concert Backgrounder (Ex. 1006)

Concert Backgrounder discloses the product platform of CoNCERT Pharmaceuticals. Ex. 1006, 2. Concert Backgrounder explains the potential benefits of deuterium modification, including improved safety, better tolerability, and enhanced efficacy. *Id.* at 3. Concert Backgrounder states, however, that "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*, [so] CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated." *Id.*

4. Analysis

As a preliminary matter, Patent Owner challenges whether Petitioner has satisfied its initial burden of showing that Jakafi Label is a printed publication. Prelim. Resp. 27–29. Because Petitioner has not satisfied its initial burden, Patent Owner argues that this ground must fail.

We agree with Patent Owner. We have often required Petitioner to come forward with sufficient evidence to make a threshold showing that the reference relied upon constitutes a printed publication. *See, e.g.*, *Symantec Corp. v. Trs. of Columbia Univ.*, IPR2015-00371, at 5–9 (PTAB June 17, 2015) (Paper 9); *Temporal Power, Ltd. v. Beacon Power, LLC*, IPR2015-00146, at 8–11 (PTAB Apr. 27, 2015) (Paper 10); *Dell, Inc. v. Selene Comm'n Techs., LLC*, IPR2014-01411, at 21–22 (PTAB Feb. 26, 2015) (Paper 23). Whether a reference qualifies as a "printed publication" involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The key inquiry is whether the reference was made "sufficiently accessible to the public interested in the art" before the critical date. *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989); *In re Wyer*, 655 F.2d 221, 226 (CCPA 1981). A reference is considered "publicly

accessible" upon a satisfactory showing that the document has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." *Kyocera Wireless Corp. v. ITC*, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (citation and internal quotation marks omitted).

Petitioner simply asserts that Jakafi Label "was first published in November of 2011. Thus, the publication is prior art under at least pre-AIA 35 U.S.C. §102(a)." Pet. 27. Petitioner cites no evidence to support its assertion that Jakafi Label was published in November 2011, let alone whether it was publicly accessible or disseminated to the public. We note that Petitioner's declarant states that Jakafi Label was first approved by the FDA in 2011 and, therefore, a person of ordinary skill in the art "would have had access to this prescribing information as of 2011." Ex. 1002 ¶ 67. But Petitioner does not cite this testimony in the Petition to support the argument that Jakafi Label is a printed publication.[5] Given the absence of any supporting evidence, we could, for this reason alone, find that Petitioner has not satisfied its initial burden of showing Jakafi Label was publicly accessible in November 2011.

Even if we were to consider Dr. Guengerich's testimony, we would still find Petitioner's argument insufficient to satisfy its initial burden. That

[5] We acknowledge that Petitioner cites Dr. Guengerich's testimony as support for the argument that "a [person of ordinary skill in the art] would have understood the compound to be a particularly effective and relatively safe compound for use in a pharmaceutical composition." Pet. 29. But this argument relates to the "Teachings of the Art and Motivation to Combine," and says nothing about whether Jakafi Label was publicly accessible. *See id.*

the FDA approved Jakafi Label in 2011 says nothing about how Jakafi Label was disseminated or otherwise made available to the public. We are not persuaded by Dr. Guengerich's conclusory statement that a person of ordinary skill in the art would have had access to this prescribing information as of 2011. Dr. Guengerich has not attested to any personal knowledge or dissemination of Jakafi Label in 2011. Nor has Dr. Guengerich directed us to any source-identifying information from the FDA (e.g., a copy of the document from the FDA's website) that would support Petitioner's contention that Jakafi Label was publicly accessible as of November 2011. In light of his unsupported assertions, we give little to no weight to Dr. Guengerich's conclusory testimony that Jakafi Label constitutes prior art.[6] *See* 37 C.F.R. § 42.65(a) (stating opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight"); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for an expert opinion "may render the testimony of little probative value in a validity determination"); *see also Sandoz Inv. v. AbbVie Biotech. Ltd.*, IPR2017-01824, at 5–9 (PTAB Feb. 9, 2018) (Paper 14) (finding petitioner failed to meet its initial burden of production to establish a drug package insert is a printed publication).

[6] Whether a reference constitutes a printed publication is Petitioner's burden to establish. Petitioner must provide a threshold amount of evidence to support its contention that the Jakafi label is prior art to the challenged claims. Although we acknowledge the issues raised in our colleague's dissent, we are not inclined to assume facts in support or make such arguments on behalf of Petitioner.

Having considered the arguments and evidence, we determine Petitioner has not satisfied its initial burden of coming forward with sufficient evidence to make a threshold showing that Jakafi Label constitutes a prior art printed publication. Accordingly, we also determine Petitioner has failed to establish a reasonable likelihood that it would prevail in its challenge that the claims of the '149 patent are unpatentable over Jakafi Label, Shilling, and Concert Backgrounder.

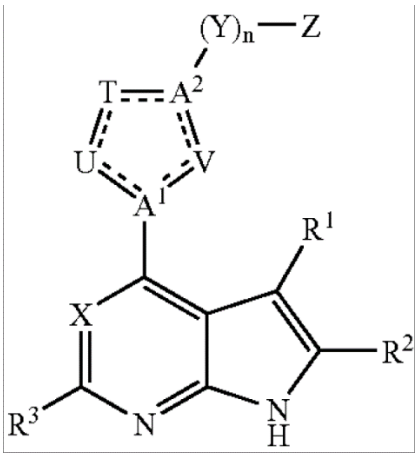
E. Obviousness over Rodgers, Shilling, and Concert Backgrounder

Petitioner asserts that claims 1–15 of the '149 patent are unpatentable as obvious over the combination of Rodgers, Shilling, and Concert Backgrounder. Pet. 50–55. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 27–59. On this record, we determine that Petitioner has established a reasonable likelihood of prevailing on this assertion.

We incorporate here our findings and discussion above regarding the disclosures of Shilling and Concert Backgrounder.

1. Rodgers (Ex. 1007)

Rodgers relates to heteroaryl substituted pyrrolo[2,3-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrimidines that modulate the activity of Janus kinases and are useful in treating diseases related to the activity of Janus kinases. Ex. 1007, 1:18–22. Rodgers discloses compounds of Formula I, including pharmaceutically acceptable salt forms or prodrugs:



Id. at 7:20–37. Rodgers discloses numerous possibilities for each constituent member of Formula I. *Id.* at 7:38–11:20. Rodgers states that its invention includes all stereoisomers, such as enantiomers and diastereomers (unless otherwise indicated). *Id.* at 31:32–34. Compounds of the invention also include "all isotopes of atoms occurring in the intermediates or final compounds. . . . For example, isotopes of hydrogen include tritium and deuterium." *Id.* at 32:13–17. Claims 1–3 recite compounds encompassing both ruxolitinib and its isomer. *Id.*, claims 1–3.

2. Whether Concert Backgrounder Is a Printed Publication

Like Jakafi Label, Patent Owner challenges whether Petitioner has met its initial burden of showing Concert Backgrounder is a printed publication. In contrast to Jakafi Label, we find Petitioner has offered a threshold amount of evidence sufficient to meet its initial burden of production.

Petitioner asserts Concert Backgrounder was publicly accessible by at least January 27, 2009, as shown in the cached WebCite page (Ex. 1016), which was "readily accessible to the public as indicated by the WebCite description of its services (Ex. 1017)." Pet. 27–28. Petitioner further notes that the accessibility of Concert Backgrounder is evidenced by its use in a

law review article published in 2009, citing the same WebCite page relied on by Petitioner. *Id.* at 28 (citing Ex. 1018, 66 n.268). Moreover, Concert Backgrounder was cited in an International Search Report for a Concert PCT application. *Id.*; Ex. 1021. According to the International Search Report, the WebCite Concert Backgrounder page was accessed on May 12, 2011. Ex. 1021, 3.

On this record, we are persuaded that Petitioner has made a sufficient showing regarding the public accessibility of Concert Backgrounder before the filing date of the challenged claims. Although we agree with Patent Owner that availability on the internet alone is not sufficient to show public accessibility, we find the corroborating evidence offered by Petitioner is sufficient to carry its initial burden. Patent Owner argues that the Petition is devoid of evidence regarding how the author of the law review article or the examiner located the Concert Backgrounder document. Prelim. Resp. 31–32. We note that the author of the law review article appears to be a "person[] interested and ordinarily skilled in the subject matter or art" of the '149 patent. *Kyocera Wireless*, 545 F.3d at 1350; Ex. 1018, 22 n.* (stating that the author has a Master's degree in chemistry and "has over eight years of experience as a synthetic organic chemist within the pharmaceutical industry"). Despite the absence of explanation as to how the reference was found, we are persuaded that the fact that two separate sources cite the archived Concert Backgrounder page before the filing date of the '149 patent is sufficiently probative of the public accessibility of the reference to meet Petitioner's initial burden.

Petitioner is not required in the Petition to conclusively establish by a preponderance of the evidence that Concert Backgrounder is a printed publication. Rather, Petitioner must make a threshold showing to establish a

reasonable likelihood that it will prevail on its assertion that it is. Considering the argument and evidence as a whole, we are persuaded that Petitioner has made that threshold showing for this reference. We note, however, that we have not made a final determination as to the public accessibility of Concert Backgrounder.

3. Obviousness Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We generally follow a two-part inquiry to determine whether a new chemical compound would have been obvious over particular prior art compounds. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012). First, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* at 1291. Second, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1292.

(a) Lead Compound

A lead compound is defined as "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity

and obtain a compound with better activity." *Otsuka* at 1291 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Stated another way, "a lead compound is 'a natural choice for further development efforts.'" *Id.* (citing *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). Importantly, the analysis of whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound "is guided by evidence of the compound's pertinent properties," including "positive attributes such as activity and potency," "adverse effects such as toxicity," and "other relevant characteristics in evidence." *Id.* at 1292.

Here, Petitioner does not expressly conduct a lead compound analysis. Instead, Petitioner asserts that the claims are obvious because Rodgers teaches a genus of deuterated ruxolitinib compounds and Shilling teaches that oxidative metabolism occurs almost entirely on the cyclopentyl ring at Y^2 and Y^3. Pet. 50–53 (citing Ex. 1002 ¶ 134). Moreover, Petitioner asserts that Concert Backgrounder explains that deuterium substitution "has the potential to create new chemical entities with improved safety, tolerability, and efficacy" and that deuterium compounds useful for this technique are "based on drugs with known efficacy and safety that address clinically validated targets." *Id.* at 51–52 (citing Ex. 1006, 2; Ex. 1002 ¶¶ 71–73, 136). According to Dr. Guengerich, Concert Backgrounder also teaches that compounds should be selected that have known "metabolic 'hot spots'" and should be deuterated at some or all of these metabolic hot spots. Ex. 1002 ¶ 136. Thus, Petitioner asserts that a person of ordinary skill in the art "would have been motivated to apply the techniques disclosed in the Concert Backgrounder to ruxolitinib and/or the deuterated ruxolitinib of Rodgers because ruxolitinib was a claimed compound of the invention in Rodgers

and ruxolitinib contained well-identified sites of oxidative metabolism in *in vivo* metabolism, as shown in Shilling." Pet. 54 (citing Ex. 1002 ¶¶ 135–136).

In response, Patent Owner argues that Petitioner provides no reason why a person of ordinary skill in the art would have specifically chosen ruxolitinib as a lead compound over the hundreds of other compounds recited in Rodgers. Prelim. Resp. 35–36. Patent Owner further asserts that candidates for deuteration include drugs that "give rise to undesirable metabolites, are cleared from the bloodstream too quickly, are metabolically broken down in the intestines or liver before reaching the bloodstream, or interfere with the clearance of other medications a patient is taking." *Id.* at 36 (quoting Ex. 1013, 3). Because Petitioner does not identify anything in the cited references that raises any such issue for ruxolitinib, Patent Owner argues that Petitioner's argument suffers from hindsight bias. *Id.*

We are persuaded on this record that a person of ordinary skill in the art would have chosen ruxolitinib as a lead compound. It is "the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Otsuka*, 678 F.3d at 1292–93. As Petitioner notes, Rodgers expressly claims ruxolitinib and its isomers. Pet. 50; Ex. 1007, claims 1–3. Moreover, Shilling states that ruxolitinib is "a potent, selective inhibitor of Janus tyrosine kinase ½ and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Ex. 1005, Abstract. On reconsideration of this record, we are persuaded that Rodgers and Shilling's teachings of these "useful properties" of ruxolitinib would have led a person of ordinary skill in the art to choose ruxolitinib as a lead compound to make structurally similar compounds. *See Otsuka*, 678 F.3d at 1292–93.

(b) Reason to Make the Claimed Compound

Even if ruxolitinib were chosen as a lead compound, Patent Owner argues that Petitioner does not identify a persuasive reason to modify ruxolitinib with deuterium. Prelim. Resp. 38–39. Petitioner contends that a person of ordinary skill in the art would have been motivated to deuterate ruxolitinib "potentially to obtain superior ADME properties." Pet. 32. But Patent Owner notes that Petitioner has not identified any specific ADME property of ruxolitinib that would have motivated a person of ordinary skill in the art to improve it. Prelim. Resp. 39.

Although we agree that Petitioner has not identified any specific property of ruxolitinib that a person of ordinary skill in the art would have known needed improvement, we have reconsidered our prior findings and acknowledge that the law does not require express motivation to be found in the art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility . . . ."). According to the Federal Circuit, "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

Dr. Guengerich testifies that "[g]iven the similarities in activity of deuterated analogs in general, it would have been obvious to use the deuterated ruxolitinib analogs in a pharmaceutical composition and expect at least the same efficacy as ruxolitinib. Ex. 1002 ¶ 88; *see also id.* ¶¶ 91–92 ("Given the known efficacy and safety of ruxolitinib, the deuterated analogs claimed in the '149 Patent would have been expected to possess at least a

similar efficacy and safety profile to that of ruxolitinib."). As support, Dr. Guengerich cites an article quoting Patent Owner's chief executive officer, who states, "[W]e've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it." Ex. 1013,[7] 5.

Patent Owner argues that Petitioner fails to explain why a person of ordinary skill in the art would have "gone through the time and expense of making deuterated ruxolitinib analogs only to obtain something very similar to ruxolitinib itself." Prelim. Resp. 39. Patent Owner also argues that Petitioner has not established a motivation to make the tetra-deuterated analogs. Prelim. Resp. 40. Shilling teaches that the major metabolites of ruxolitinib are formed by oxidation at both the 2- and 3-positions of the cyclopentyl ring. Ex. 1005, 6, 8. Shilling also teaches that the plasma concentration of metabolites formed by oxidizing at the 2- and 3-positions are comparable. *Id.* According to Patent Owner and its declarant, Dr. Baillie, a person of ordinary skill in the art would not have had a reasonable expectation that deuterating only one of the two positions would result in a significant kinetic isotope effect, due to the possibility of metabolic switching. Prelim. Resp. 40–41; Ex. 2002 ¶¶ 72–75.

Both of Patent Owner's arguments are premised on the notion that Petitioner must show a person of ordinary skill in the art would not have expected deuterated analogs of ruxolitinib to have improved properties over ruxolitinib. However, Petitioner can show a motivation to make deuterated

---

[7] Amanda Yarnell, *Heavy-Hydrogen Drugs Turn Heads, Again*, 87 CHEMICAL & ENGINEERING NEWS 36–39 (2009). We note that Dr. Guengerich cites the page number provided pursuant to 37 C.F.R. § 42.63(d)(2).

ruxolitinib by demonstrating a person of ordinary skill in the art would have expected deuterated ruxolitinib to have "similar properties" as ruxolitinib. *See Dillon*, 919 F.2d at 693 ("The art provided the motivation to make the claimed compositions in the expectation that they would have similar properties."). On this record, Petitioner has shown sufficiently that a person of ordinary skill in the art would have expected deuterated ruxolitinib to have similar properties to ruxolitinib, and thus a reason to modify ruxolitinib.

(c) Reasonable Expectation of Success

Petitioner asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in combining Rodgers, Shilling, and Concert Backgrounder to reach compounds encompassed by the claims for several reasons. Pet. 54; *see also id*. at 32–39. For example, Petitioner argues that a person of ordinary skill in the art could have easily synthesized such compounds and would have expected those compounds to perform at least as well as ruxolitinib, which is sufficient to render the claims prima facie obvious. Pet. 33 (citing Ex. 1002 ¶¶ 91–93, 104–105); *Aventis*, 499 F.3d at 1301; *Dillon*, 919 F.2d at 692.

Petitioner and its declarant further argue that an ordinary artisan would have expected improved metabolic stability over ruxolitinib based on Shilling and Concert Backgrounder. Pet. 33–39; Ex. 1002 ¶¶ 94–108. Shilling teaches that ruxolitinib was an ideal candidate for deuteration, as the metabolism of ruxolitinib is largely restricted to the cyclopentyl ring. Ex. 1002 ¶¶ 83–84. Concert Backgrounder discloses a prior example of deuteration, torcetrapib, where the six deuterated analogs that improved metabolic stability were the compounds that were fully deuterated at the metabolic hotspot. Ex. 1002 ¶¶ 74–77. Thus, Dr. Guengerich notes that

Concert Backgrounder states that deuteration "substantially reduced R&D risk, time, and expense," suggesting the "relative ease and predictability of producing deuterated analogs of known pharmacologically-active compounds and suggests to a [person of ordinary skill in the art] a reasonable expectation of success." *Id.* ¶ 73.

Patent Owner argues that Petitioner's arguments are at odds with the state of the art and that a person of ordinary skill in the art would have known that deuterating hotspots does not predictably lead to increased metabolic stability. Prelim. Resp. 42 (citing *Neptune Generics, LLC v. Auspex Pharms., Inc.*, IPR2015-01313, at 20–21 (PTAB Dec. 9, 2015) (Paper 25)). Patent Owner asserts that a person of ordinary skill in the art would have understood that metabolic switching can mask a kinetic isotope effect. *Id.* at 11–12. Moreover, Patent Owner provides prior art examples where deuterium modification of drugs, even at metabolic hotspots, does not improve the pharmacokinetic properties in a predictable manner. *Id.* at 12–18; Ex. 2002 ¶¶ 60–71.

At this stage of the proceeding, when faced with competing testimonial evidence that raises a genuine issue of material fact, we must view the evidence in the light most favorable to the petitioner for purposes of our Decision. 37 C.F.R. § 42.108(c). Accordingly, we are persuaded that Petitioner has made a sufficient showing that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the cited references to reach the claimed compounds. We will further evaluate the parties' competing positions after the record has been developed further at trial.

(d) Objective Indicia of Nonobviousness

An obviousness argument may be rebutted "with a showing that the claimed compound has unexpected properties." *Aventis*, 499 F.3d at 1301. As explained above, the '149 patent applicants relied on evidence of unexpected results during prosecution to overcome the examiner's obviousness rejection. *See supra*. Petitioner and its declarant directly address that evidence, asserting that the studies described by Ms. Uttamsingh were not probative of unexpected results. Pet. 40–43; Ex. 1002 ¶¶ 118–129. Patent Owner responds with the testimony of Dr. Harbeson and Dr. Baillie, describing Concert studies that demonstrate why deuterated ruxolitinib produced unexpected results. Prelim. Resp. 19–22, 48–58; Ex. 2001 ¶¶ 10–18; Ex. 2002 ¶¶ 41–59. For example, Patent Owner and its declarant, Dr. Baillie, assert that CTP-543 (i.e., compound 111 of the '149 patent, Ex. 2001 ¶ 4) has two unexpected clinical advantages over ruxolitinib: (1) an increased therapeutic window; and (2) increased clinical response at a given dose. Prelim. Resp. 54–58; Ex. 2002 ¶¶ 49–53.

Once again, we are faced with competing testimony. Accordingly, we view the competing testimony, here in regard to unexpected results, in the light most favorable to Petitioner for purposes of our Decision. 37 C.F.R. § 42.108(c). In that light, the testimony persuades us that Petitioner has made a sufficient showing that the allegedly unexpected results of the claimed compounds do not outweigh the evidence in support of obviousness.

In conclusion, having considered the parties' arguments and evidence, we determine Petitioner has shown a reasonable likelihood of prevailing in its assertion that claims 1–15 of the '149 patent are unpatentable as obvious over Rodgers, Shilling, and Concert Backgrounder.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1–15 of the '149 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following ground:

Claims 1–15 as unpatentable as obvious over Rodgers, Shilling, and Concert Backgrounder.

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized.

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

Trials@uspto.gov
571.272.7822

Paper No. 14
Entered: April 9, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2017-01256
Patent 9,249,149 B2

Before LORA M. GREEN, MICHAEL J. FITZPATRICK, and TINA E. HULSE, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*, dissenting in part.

I dissent in part from the opinion of the Board. Specifically, I dissent from its holding that "Petitioner has not satisfied its initial burden of coming forward with sufficient evidence to make a threshold showing that Jakafi Label constitutes a prior art printed publication." *See supra*, § II.D.4.

"Jakafi Label" is a term that we assigned Exhibit 1004 in our Decision Denying Institution. Paper 9, 6 n.1. In its Petition, Petitioner refers to it as "Jakafi® (ruxolitinib) Prescribing Information (Ex. 1004)." Pet. 2.

The Petition asserts that "[t]he Jakafi® (ruxolitinib) Prescribing Information (Ex. 1004) was first published in November of 2011." Pet. 27. The face of Exhibit 1004 is consistent with this assertion. Ex. 1004, 1 (stating: "JAKAFI™ (ruxolitinib) tablets, for oral use Initial U.S. Approval: 2011" and "Revised: 11/2011"). The Petition also asserts that the drug to which Exhibit 1004 pertains, ruxolitinib, "was a well-established, pharmaceutical first approved by the FDA [i.e., Food and Drug Administration] in November 2011 under the tradename Jakafi®." Pet. 23 (citing Ex. 1004; Ex. 1002 ¶63).

Thus, Petitioner asserts, with supporting evidence (Ex. 1004 and Ex. 1002 ¶63), that in November 2011 both of the following occurred: (1) ruxolitinib was approved by the FDA; and (2) prescribing information for ruxolitinib was published. It is clear enough to me, from these statements and from my understanding of the FDA drug approval process, that Petitioner asserts Exhibit 1004 to have been published by the FDA in November 2011 concurrent with its approval of the drug. *See Bayer Schering Pharma AG v. Lupin*, Ltd., 676 F.3d 1316, 1322 (Fed. Cir. 2012) ("The FDA-approved label for an approved drug indicates whether the FDA has approved a particular method of use for that drug."); *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 36 (1st Cir. 2015) ("In order to approve an NDA or sNDA, the FDA must determine, based on a fair evaluation of all material facts, that the proposed label is not false or misleading in any particular. After approval, the manufacturer may distribute the drug without violating federal law as long as it uses the FDA-

approved label.") (citations and internal quotation marks omitted). Thus, Petitioner has identified both the publisher and publication date of Exhibit 1004. I am also satisfied by the form and content of Exhibit 1004 that, in fact, it is the prescribing information for ruxolitinib as published by the FDA in November 2011. *See, e.g.*, Ex. 1004, 1 ("JAKAFI™ (ruxolitinib) tablets, for oral use Initial U.S. Approval: 2011" and "Revised: 11/2011"), 23 ("This Patient Information has been approved by the U.S. Food and Drug Administration."). If Exhibit 1004 is not an accurate copy of what the FDA published when it approved ruxolitinib in November 2011 or if the FDA did not approve ruxolitinib in November 2011, Patent Owner could easily prove as much at trial. *See* https://www.accessdata.fda.gov/scripts/cder/daf/.[8]

In addition, Dr. Guengerich testified that because "Jakafi® (ruxolitinib)" was "approved by the FDA in 2011," a person of ordinary skill in the art "would have had access to this prescribing information as of 2011 and would have understood that ruxolitinib was a known FDA-approved drug with a known efficacy and safety that addressed a clinically validated

[8] It is also true that, if Exhibit 1004 is what Petitioner represents it to be, it would have been easy for Petitioner to prove *decisively*, and likely to satisfaction of my colleagues, that Exhibit 1004 is a prior art printed publication by submitting evidence of its provenance, e.g., that it was downloaded or printed directly from the FDA's website.

target." Ex. 1002 ¶ 67 (citing Ex. 1004).[9]

I think Petitioner made a sufficient showing that Exhibit 1004 is both a printed publication and prior art to the challenged claims of the '149 patent. Accordingly, I would have considered further whether there is a reasonable likelihood of Petitioner prevailing on the ground that the challenged claims would have been obviousness in view of Jakafi Label, Shilling, and Concert Backgrounder.

[9] As my colleagues note, Petitioner cites to paragraph 67 of Exhibit 1002 in an argument presented under the following title: "Teachings of the Art and Motivation to Combine." *See supra* 13 n.5; Pet. 29. I disagree, however, that Petitioner's argument there "says nothing about whether Jakafi Label was publicly accessible." *See supra* 13 n.5. The argument in question states the following: "Jakafi® (ruxolitinib) Prescribing Information demonstrates that, not only was ruxolitinib a known compound as of June 15, 2012, but it was an ***FDA-approved*** known compound. Ex. 1004. Thus, a POSA would have understood the compound to be a particularly effective and relatively safe compound for use in a pharmaceutical composition. Ex. 1002, ¶ 67." Pet. 29.

PETITIONER:

FOLEY & LARDNER LLP
Stephen B. Maebius
Michele M. Simkin
smaebius@foley.com
msimkin@foley.com

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
Thomas L. Irving
Mark J. Feldstein
Maureen D. Queler
Christopher McDavid
tom.irving@finnegan.com
mark.feldstein@finnegan.com
maureen.queler@finnegan.com
christopher.mcdavid@finnegan.com

PATENT OWNER:

GOODWIN PROCTER LLP
Cynthia Lambert Hardman
Marta E. Delsignore
Sarah J. Fischer
chardman@goodwinlaw.com
mdelsignore@goodwinlaw.com
sfischer@goodwinlaw.com